Atty Docket No: 12E-9881 0US
Client Ref: G67

#21
4/23/03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Jagdish Parasrampuria; Maxine B. Yonker; Kenneth E. Schwartz; Marc J. Gurwith
Application No.: 09/526,802

Filed: 3/16/2000

For: **DHEA Composition And Method**

Examiner: Qazi, S.

Art Unit: 1616

DECLARATION UNDER 37 C.F.R. 1.132

DECLARATION OF DR. PATRICK STAHLY

1. I, Dr. Patrick Stahly, am the Chief Operating Officer and Vice President of Research and Development for SSCI, Inc. SSCI is a contract research laboratory specializing in crystallization, characterization, and chemistry of solids. Our expertise includes polymorph screening, salt selection, analytical characterization of active pharmaceutical ingredients and dosage forms, quantitative mixture analysis, problem solving, optimization of crystallization processes, and educational short courses.

2. I have read the above-referenced patent application, including the currently pending claims, the Office Actions dated February 12, 2002 and June 14, 2002, and Chang *et al.*, J. Pharm. Sci. 84:1169-1179 (1995) (the Chang article), which is cited therein. I have been asked to comment on whether a person of ordinary skill in the art of the preparation and characterization of different polymorphic forms of compounds would interpret Chang as describing dehydroepiandrosterone (DHEA) preparations containing at least 85% form I DHEA.

3. I believe I am well qualified to address these questions, as I have devoted more than 25 years to the study of organic chemistry, including approximately 10 years studying crystallization and polymorphism. I received a Ph.D. in 1979 from the University of Maryland and immediately joined the Ethyl (later Albemarle) Corporation, where I worked for 15 years and attained the title of Senior Research Advisor. In 1995 I moved to SSCI as the Vice President of

Research and Development, acquiring the additional title of Chief Operating Officer in 1997. Thus, I have extensive, first-hand experience with the techniques relevant to the preparation and characterization of DHEA polymorphs.

4. Chang reported the characterization of the following solid forms of DHEA: three polymorphs (forms I-III), two monohydrates (forms S2 and S3), a 4:1 hydrate (form S1), and a methanol half-solvate (form S4). She also reported the observance of, but not characterization of, a form designated form V. Chang stated that crystals of "form I DHEA were prepared by dissolving excess DHEA in ethyl acetate, acetone, acetonitrile or 2-propanol with the aid of heat." Chang, page 1169, col. 2. Based on my experience, standard crystallization of DHEA out of organic solutions, such as Chang described, can yield mixtures of form I DHEA with significant amounts (*e.g.*, 30-40%) of form VI DHEA.

5. None of the analytical techniques used by Chang to characterize the DHEA polymorph preparations can distinguish between form I DHEA and form VI DHEA. Chang characterized the DHEA forms she produced using differential scanning calorimetry (DSC), thermogravimetry (TG), hot stage microscopy, X-ray powder diffractometry, Fourier transform infrared (IR) spectrometry, and Karl Fischer titration. Solution calorimetry and intrinsic dissolution rates were used to determine relative stabilities of the forms. Chang concluded that "[d]efinitive polymorph identification was based on X-ray powder diffraction patterns," and that "the purities of forms I-III and S1 are as high as 95%, and X-ray powder diffraction can potentially be employed as a method of estimating the purity of polymorphs of DHEA." These conclusions are based on data obtained from samples of the forms obtained by Chang and assumed to be pure. By comparison of the X-ray powder diffraction patterns of the samples obtained, Chang was able to recognize peaks unique to each sample, and was able to use these unique peaks to determine the purity of form I samples *only relative to the other forms known to Chang, namely forms II, III, and S1*. In fact, Chang noted that X-ray powder diffraction cannot always be used to determine purity due to peak overlap; for example, Chang stated that "forms S3 and S4 are indistinguishable...[by their] X-ray powder diffraction pattern[s]."

6. Chang erroneously believed that X-ray powder diffraction could distinguish all the DHEA polymorphs (with the possible exception of S3 and S4) and therefore used this technique to estimate the purity of DHEA polymorph preparations. Chang, page 1173, col. 2. More specifically, Chang determined the characteristic X-ray powder diffraction peaks for each of the

polymorph preparations. *Id.* Chang then performed mixing studies and determined that it was possible to detect "characteristic X-ray powder diffraction peaks of small amounts (5-10%) of a contaminating" form mixed with another form. *Id.* Based on these studies, Chang concluded that "the purities of forms I-III and S1 are as high as 95%, and X-ray powder diffraction can potentially be employed as a method of estimating the purity of polymorphs of DHEA." Chang, page 1175, col. 1. However, this conclusion rested on the assumption that Chang's preparations of forms I-III and form S1 were pure. Chang, page 1173, col. 2.

7. As a result of the work described in the present patent application, we now know that Chang's assumption was unjustified. That is, we now know that standard crystallization out of organic solvents can produce preparations containing a significant amount of form VI DHEA, in addition to form I DHEA. Further, the X-ray powder diffraction patterns of forms I and VI DHEA are so similar that mixtures of forms I and VI exhibit X-ray powder diffraction patterns indistinguishable from that exhibited by pure form I, a situation analogous to that reported by Chang for forms S3 and S4. As described in the patent application, solid state NMR, a technique not employed by Chang, was employed to distinguish form I DHEA from the previously unknown form VI DHEA. Application No. 09/526,802, page 7, lines 23-24.

8. To illustrate that a mixture of form I and form VI DHEA exhibit essentially the same X-ray powder diffraction pattern as a pure form I preparation, X-ray powder diffraction patterns of a form I:form VI mixture and pure form I are attached as Exhibits A and B. I estimate, based on the NMR spectra (described below), that the mixture contained as much as 30-40% form VI. Any comparison of X-ray powder diffraction patterns must always take into account the effect of "preferred orientation," which is the tendency of crystals to pack against each other with some degree of order as material is prepared for analysis. Preferred orientation leads to changes in relative peak intensities in X-ray powder diffraction patterns. The effect of preferred orientation is evident by comparing the X-ray powder diffraction pattern of a pure form I preparation (Exhibit B) to the X-ray powder diffraction pattern calculated from single crystal X-ray analysis data (Exhibit C). Note, for example, that a doublet is evident at about 20 °2θ in the former (Exhibit B) but the calculated pattern (Exhibit C), which does not exhibit preferred orientation effects, has only a single peak in this region because of the decreased intensity of the low-angle peak of the doublet. Unless the X-ray powder diffraction pattern of each pure form that may be present in a mixture is known, preferred orientation makes it difficult to determine if patterns exhibited by specific preparations represent

mixtures or not. The reason that the patterns of mixtures of forms I and VI and pure form I appear essentially the same is clear when one considers the X-ray powder diffraction pattern of a pure form VI preparation, which is attached as Exhibit D. Each of the significant peaks in the form VI preparation underlies a significant peak in the form I preparation. Chang indicates that the characteristic peaks for form I, in units of °2θ, are observed at 14.99°, 15.40, 17.68°, 18.05°, and 18.59. Chang, page 1173, col. 1. Exhibit D, the X-ray powder diffraction pattern for a pure form VI preparation, shows that the largest peaks observed for form VI coincide with the first four of Chang's characteristic form I peaks, and that essentially every peak in the form VI pattern occurs in regions where the form I pattern also contains peaks. Thus, X-ray powder diffraction cannot differentiate between mixtures of forms I and VI DHEA and pure form I DHEA.

9. As described in the present application, solid state, carbon-13 NMR, a technique that Chang did not use, can distinguish between a pure form I DHEA preparation, a mixture of forms I and VI, and a pure form VI DHEA preparation. The NMR spectra for each of the preparations discussed in the above paragraph are attached as Exhibits E-J. Only those portions of the specta where forms I and VI can be differentiated are shown. The chemical shift assignments are as follows:

Form	C18 (ppm)	C6 (ppm)
I	14.8, 14.1*	120.4, 118.9*
VI	14.4	118.5

* Form I is known to have two crystallographically independent molecules in the structure.

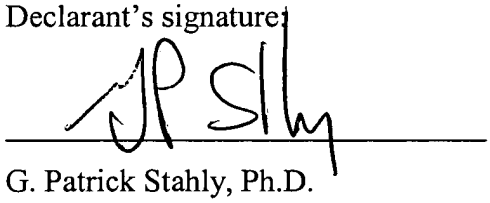
Exhibits E and F show the spectra for the form I:form VI mixture. All the peaks in the diagnostic regions are of approximately the same size. Since two peaks of each set of three result from form I, which has two crystallographically independent molecules in the structure, the ratio of the peak sizes is approximately 1:2 (form VI:form I), which is thus the ratio of the forms in the mixture. Based on this analysis, I estimate that this mixture contained approximately 30-40% form VI DHEA. This estimate assumes the NMR responses of the two forms are the same. Exhibit E shows three characteristic peaks, two (14.767 and 14.160 ppm) that are attributable to form I and one (14.403 ppm) that is attributable to form VI. Similarly, Exhibit F shows three characteristic peaks, two form

I peaks (120.352 and 118.896 ppm) and one form VI peak (118.532 ppm). Exhibits G and H are the spectra for the pure form I preparation, each of which show the two characteristic form I peaks. Exhibits I and J are the spectra for the pure form VI preparation, and these show the characteristic form VI peaks.

10. The results shown in the exhibits demonstrate that form VI present in form I DHEA preparations at levels as high as 30-40% cannot be detected by X-ray powder diffraction. Since form VI was unknown to Chang, she did not know what diagnostic analytical indicators to look for in her form I preparations that might indicate the presence of form VI. Chang's X-ray powder diffraction results do not support the conclusion that Chang's form I preparation was 95% pure. To the contrary, the results shown in the exhibits establish that Chang's form I preparations could have contained as much as 40% form VI. For this reason, it is my opinion that a person of ordinary skill in the art of the preparation and characterization of different polymorphic forms of compounds would not view Chang as describing DHEA preparations containing at least 85% form I DHEA.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Declarant's signature:



G. Patrick Stahly, Ph.D.

2/27/03

Date

EXHIBIT A

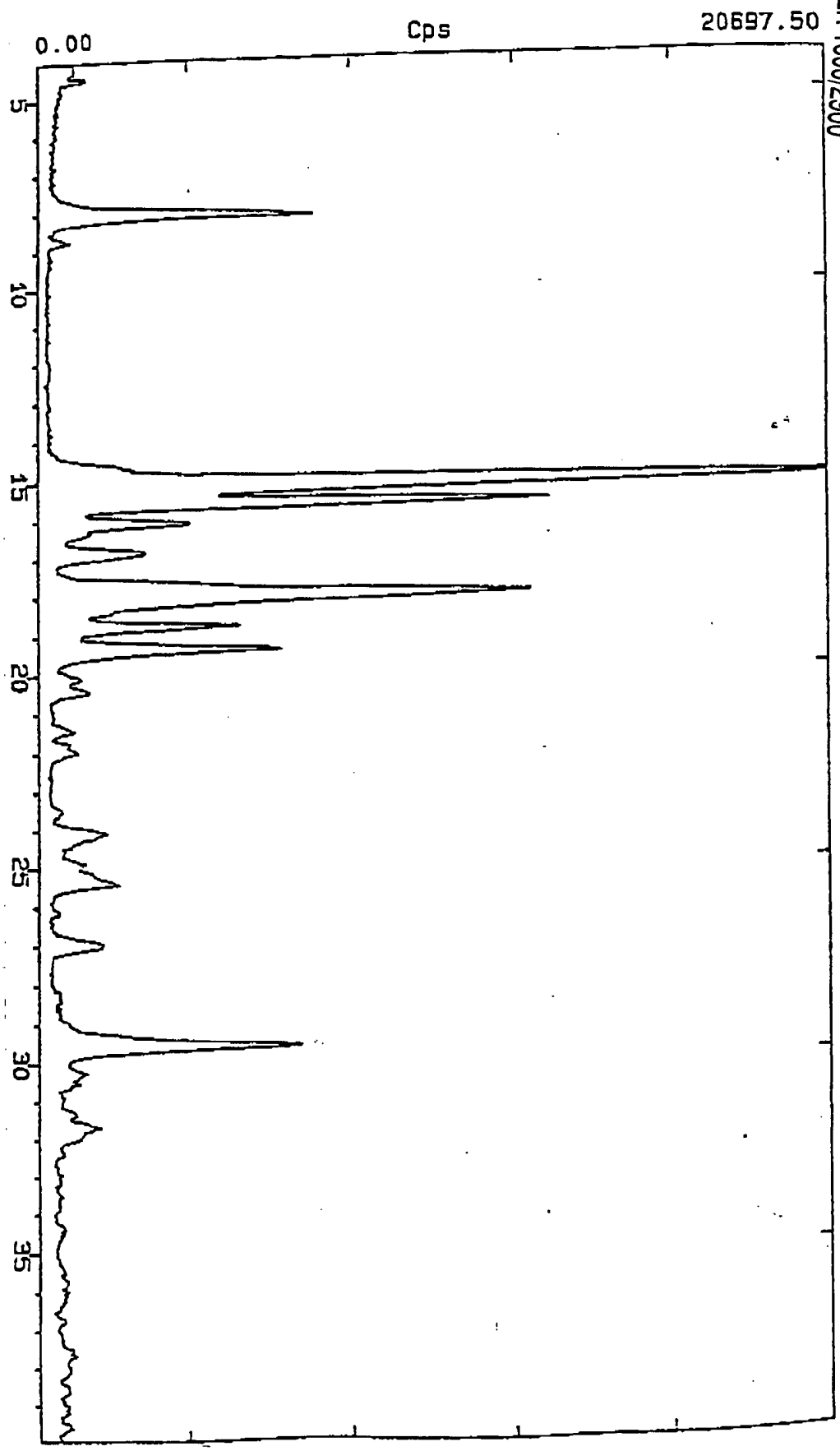


EXHIBIT B

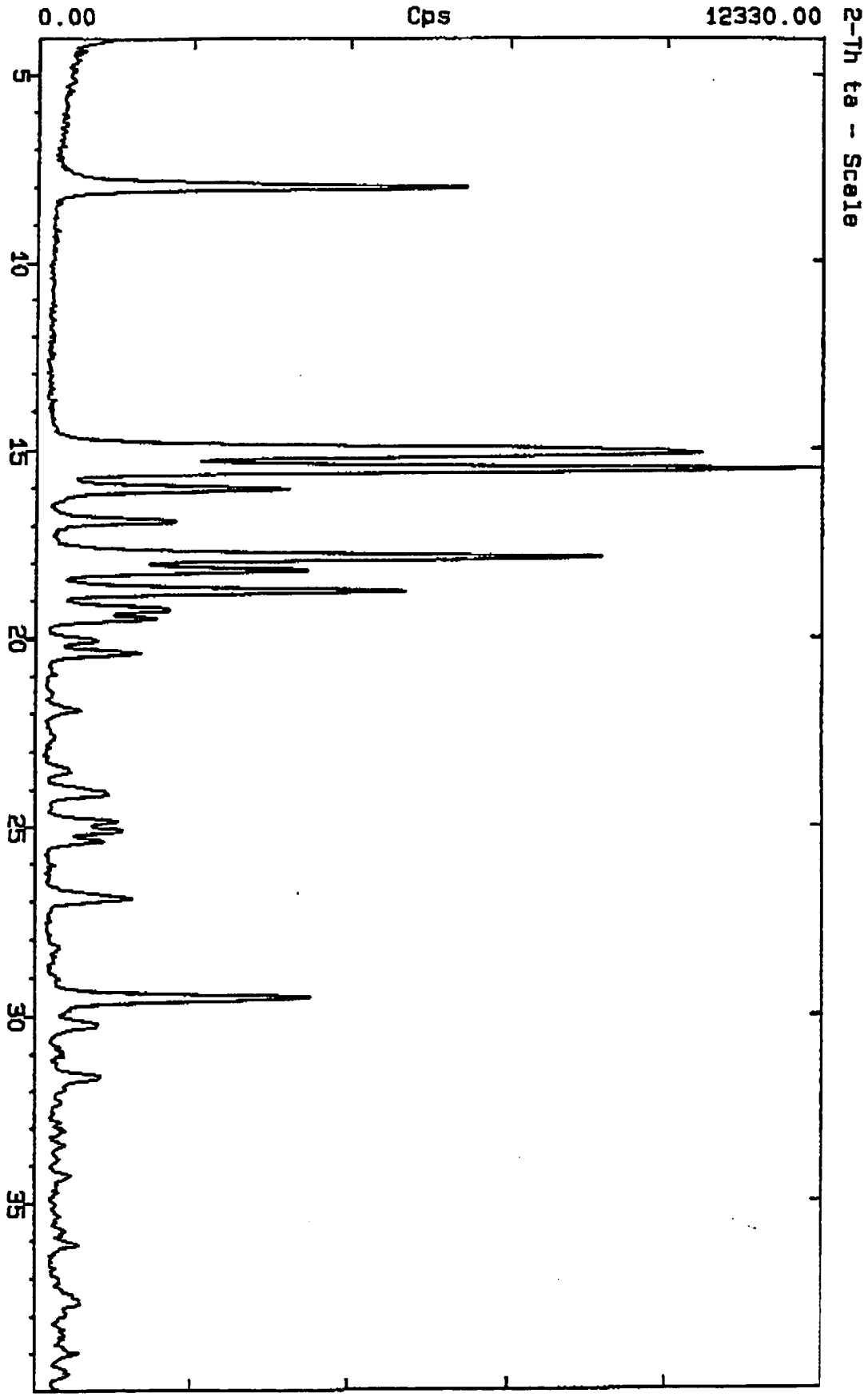
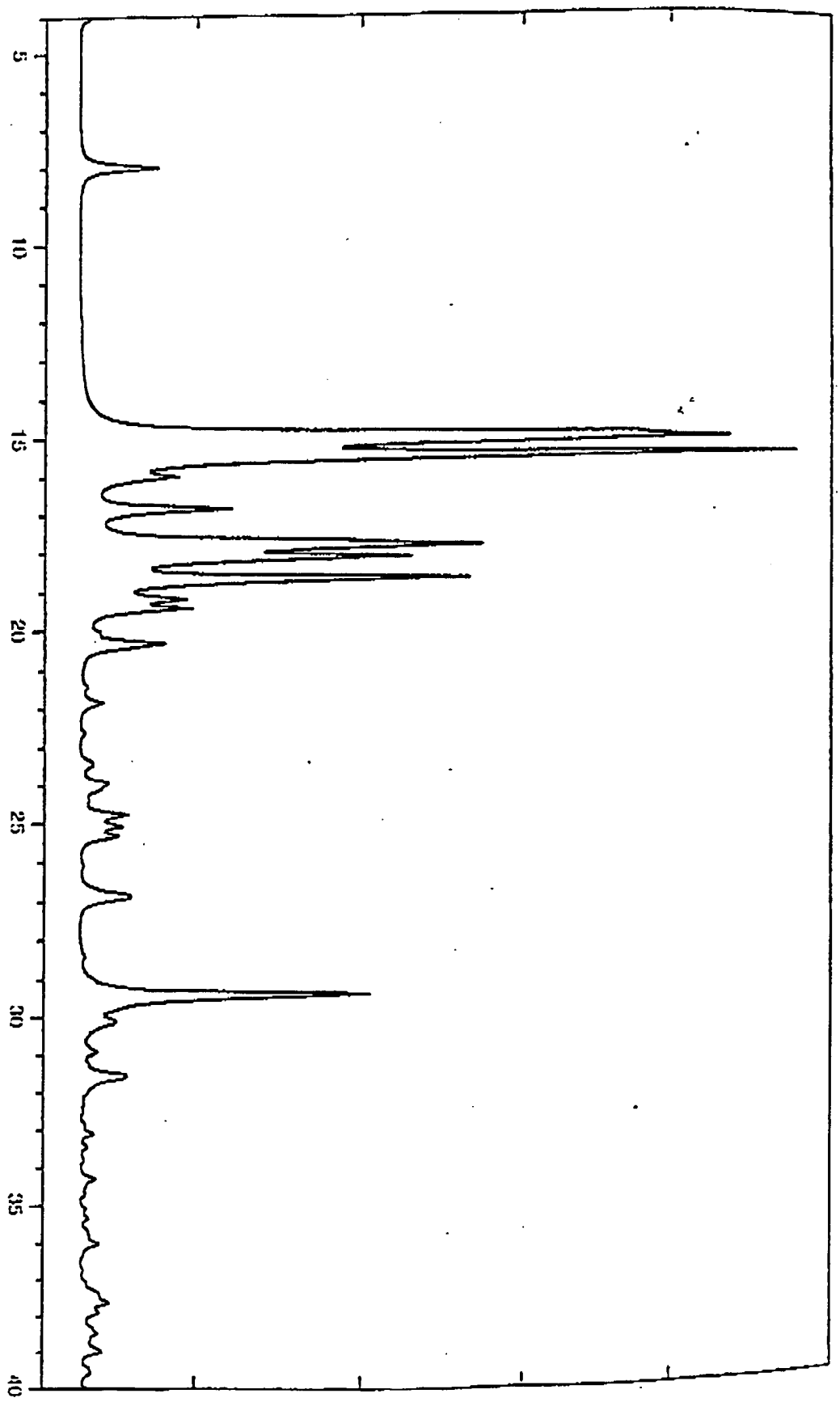


EXHIBIT C



DIEA Form FI XRPD Pattern Calculated from Single Crystal Data

EXHIBIT D

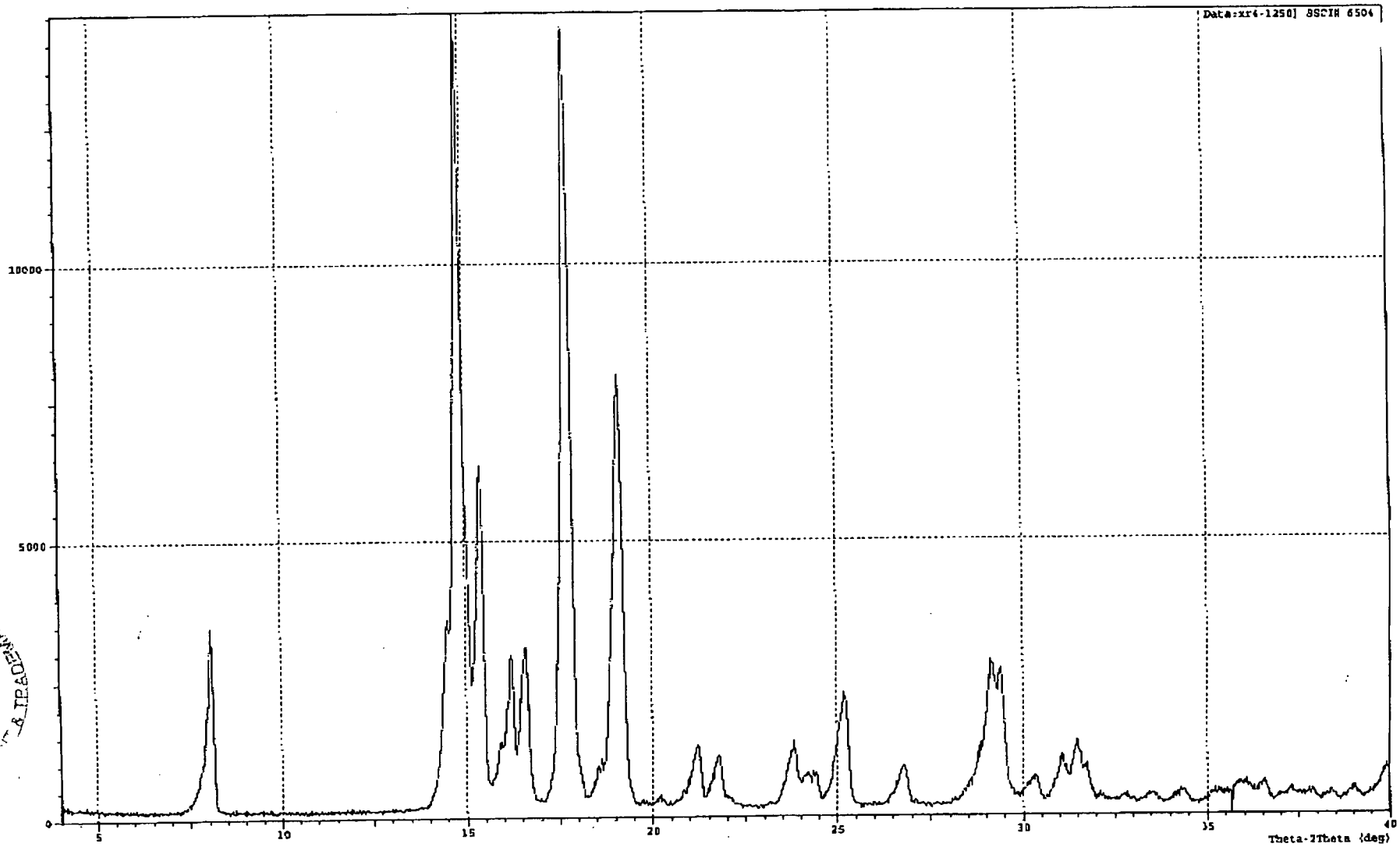


EXHIBIT E

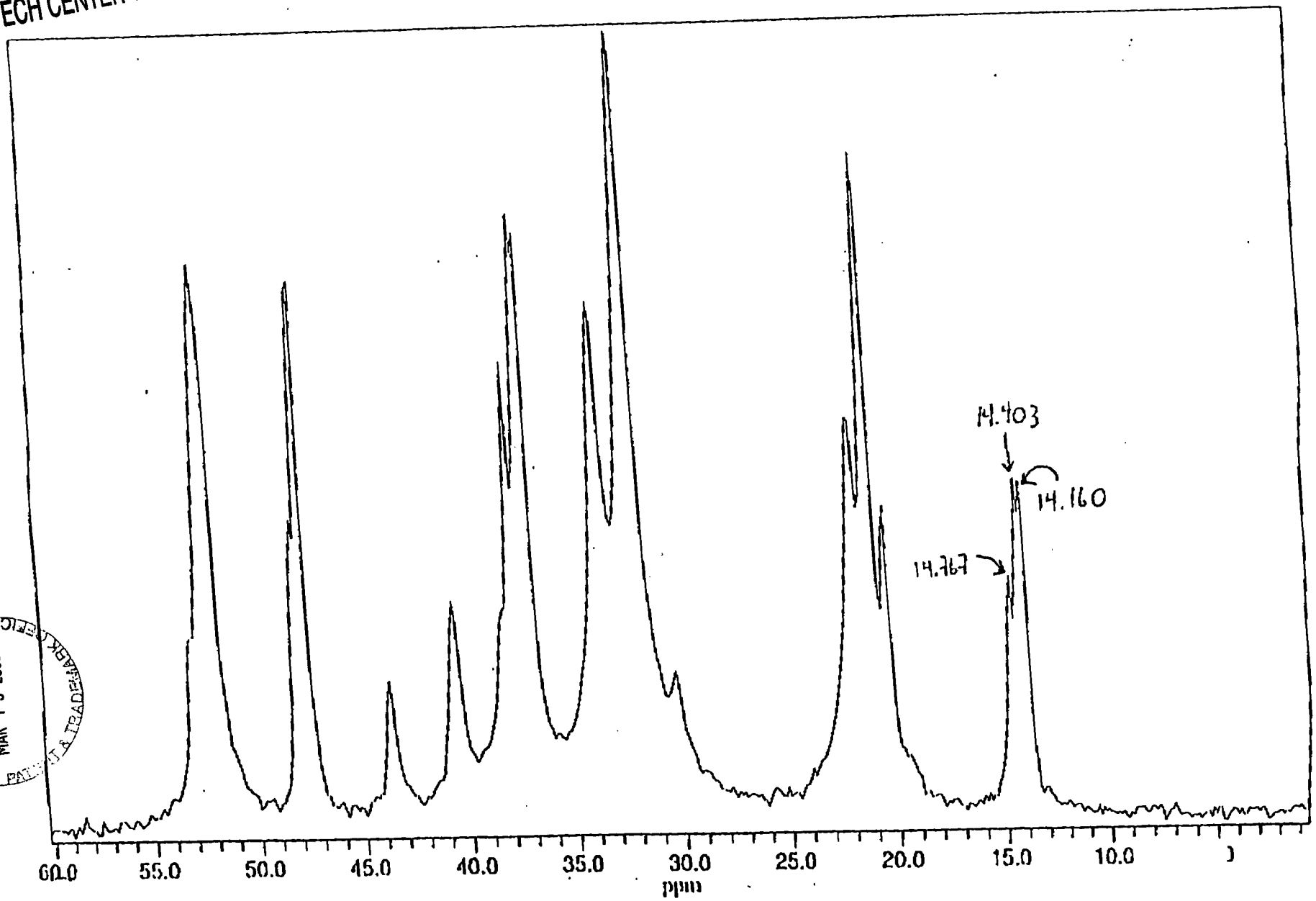


EXHIBIT F

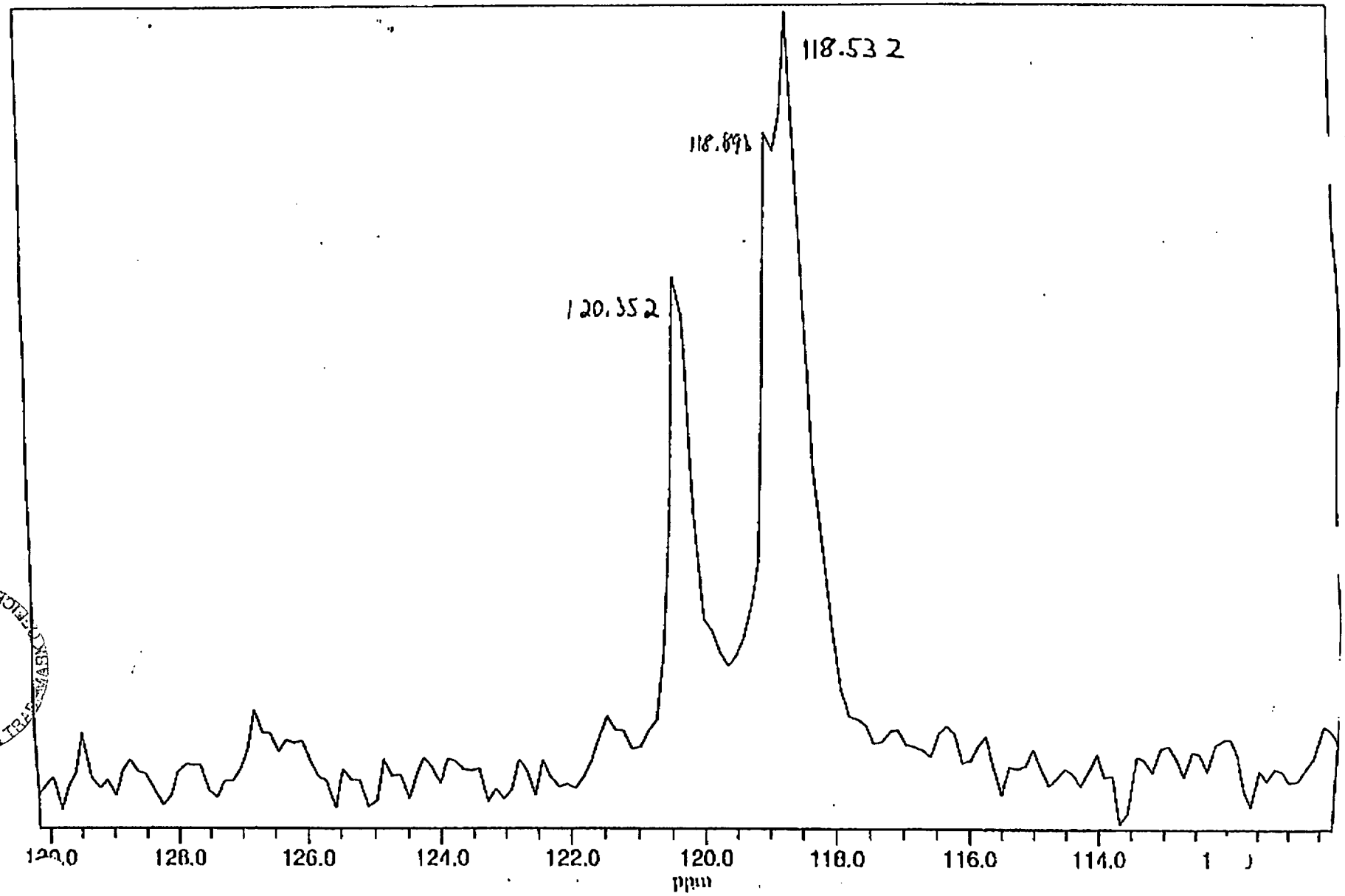


EXHIBIT G

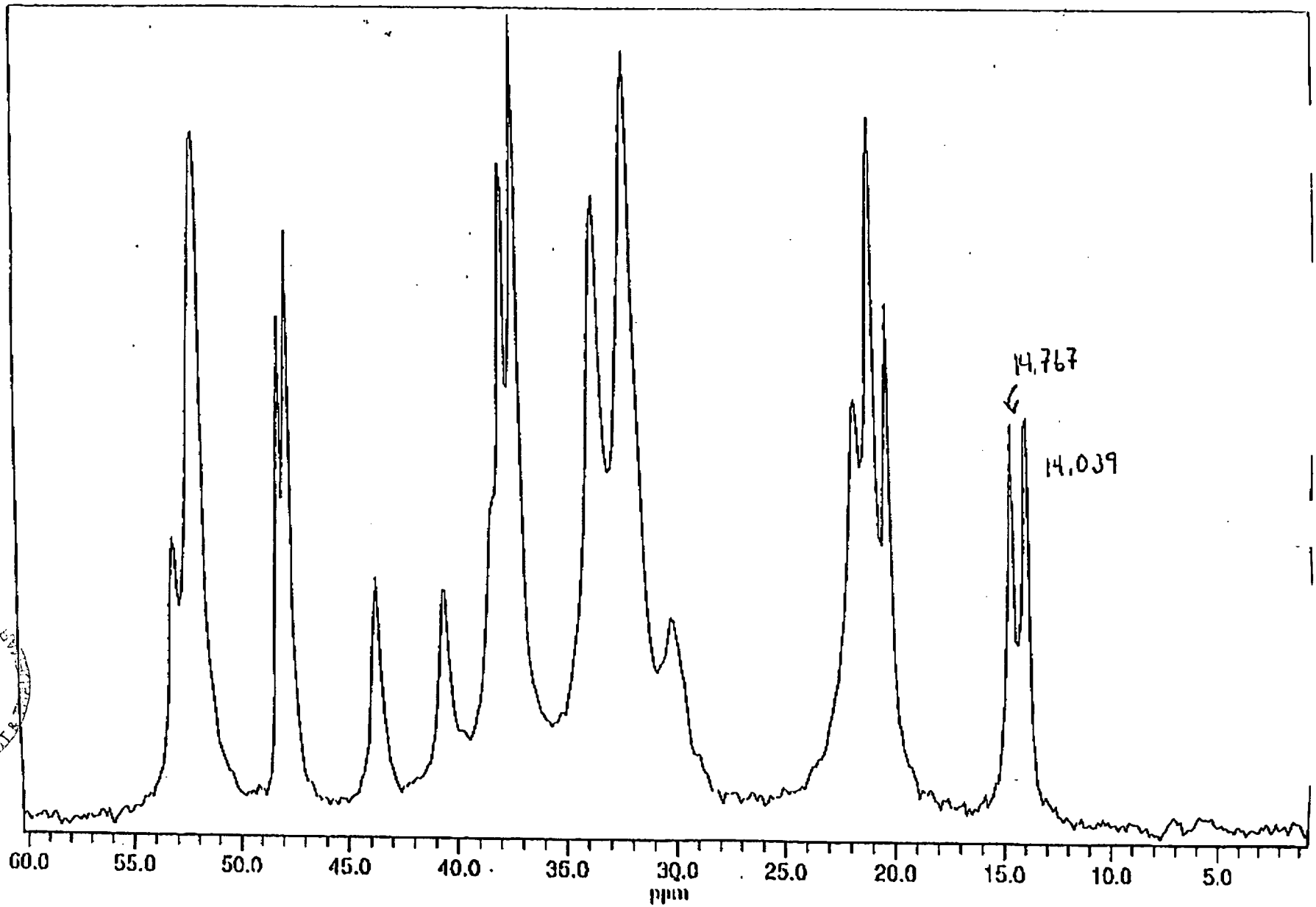
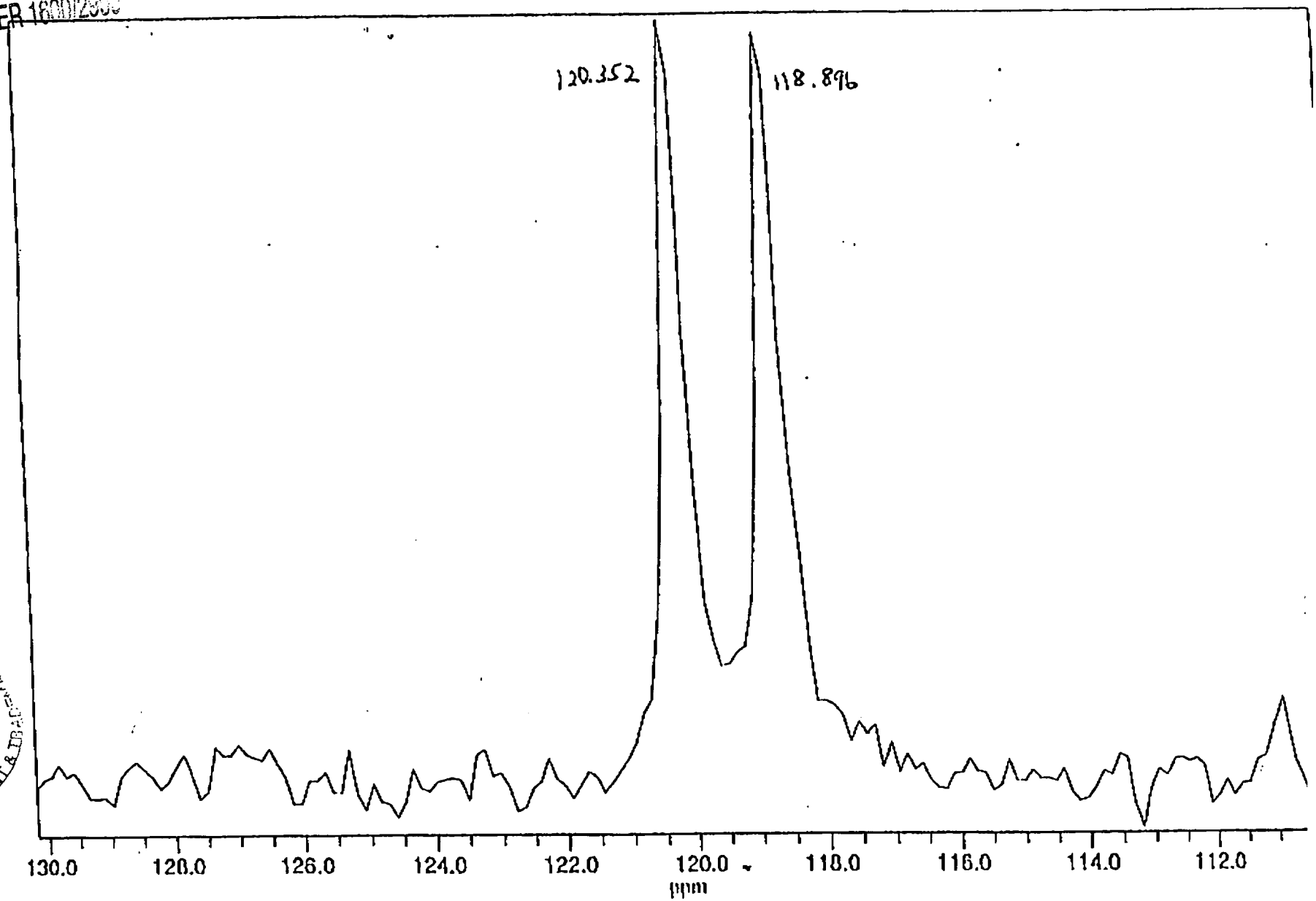


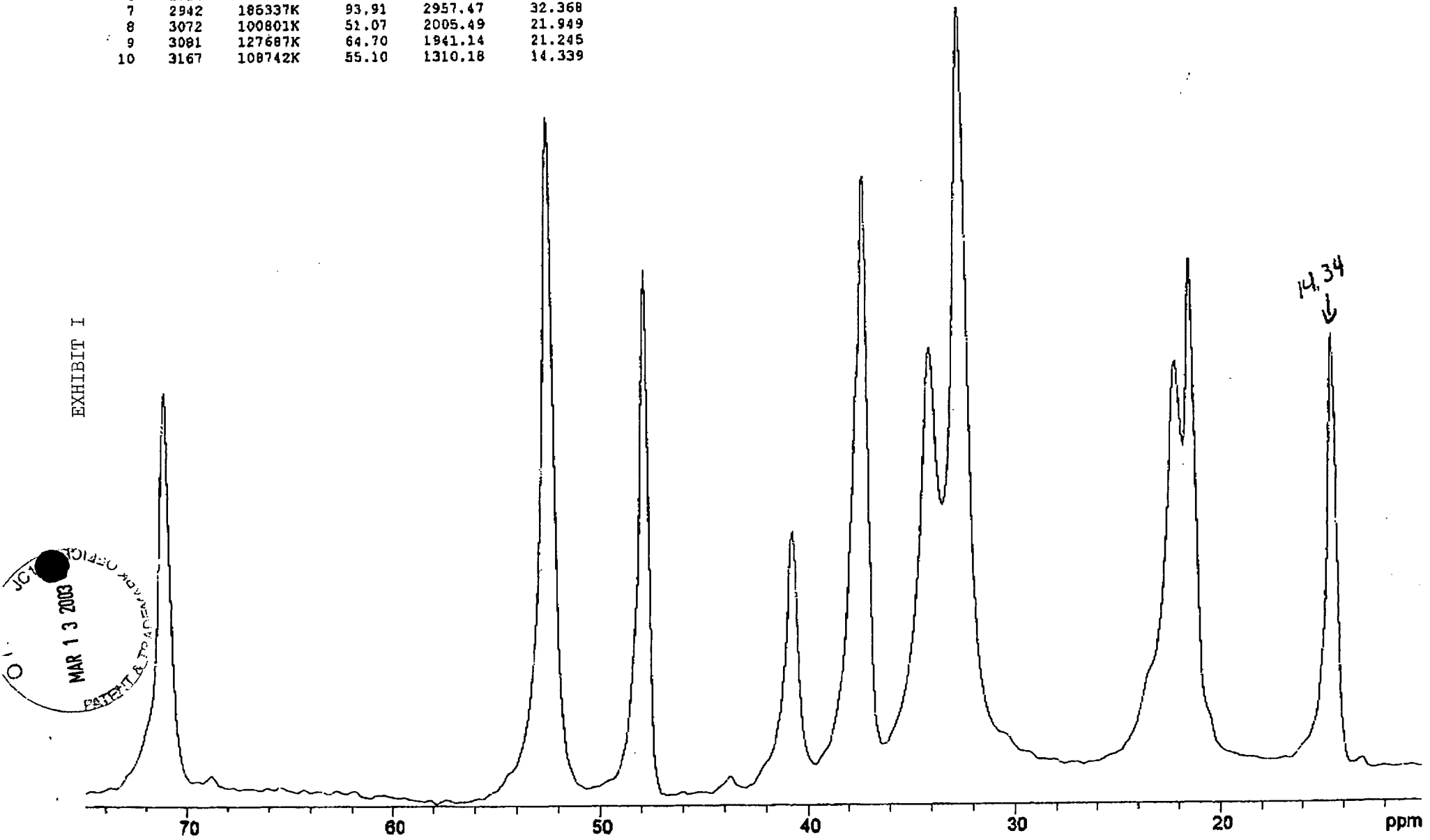
EXHIBIT H



Interpolated Peak Listing

PEAK	POINT	HEIGHT	REL. HT	HZ	PPM
1	2462	94799K	48.03	6479.82	70.919
2	2693	159969K	81.05	4788.41	52.407
3	2751	124609K	63.14	4362.72	47.748
4	2839	61577K	31.20	3714.77	40.657
5	2884	146003K	73.98	3382.45	37.019
6	2924	104233K	52.81	3089.76	33.816
7	2942	186337K	93.91	2957.47	32.368
8	3072	100801K	51.07	2005.49	21.949
9	3081	127687K	64.70	1941.14	21.245
10	3167	108742K	55.10	1310.18	14.339

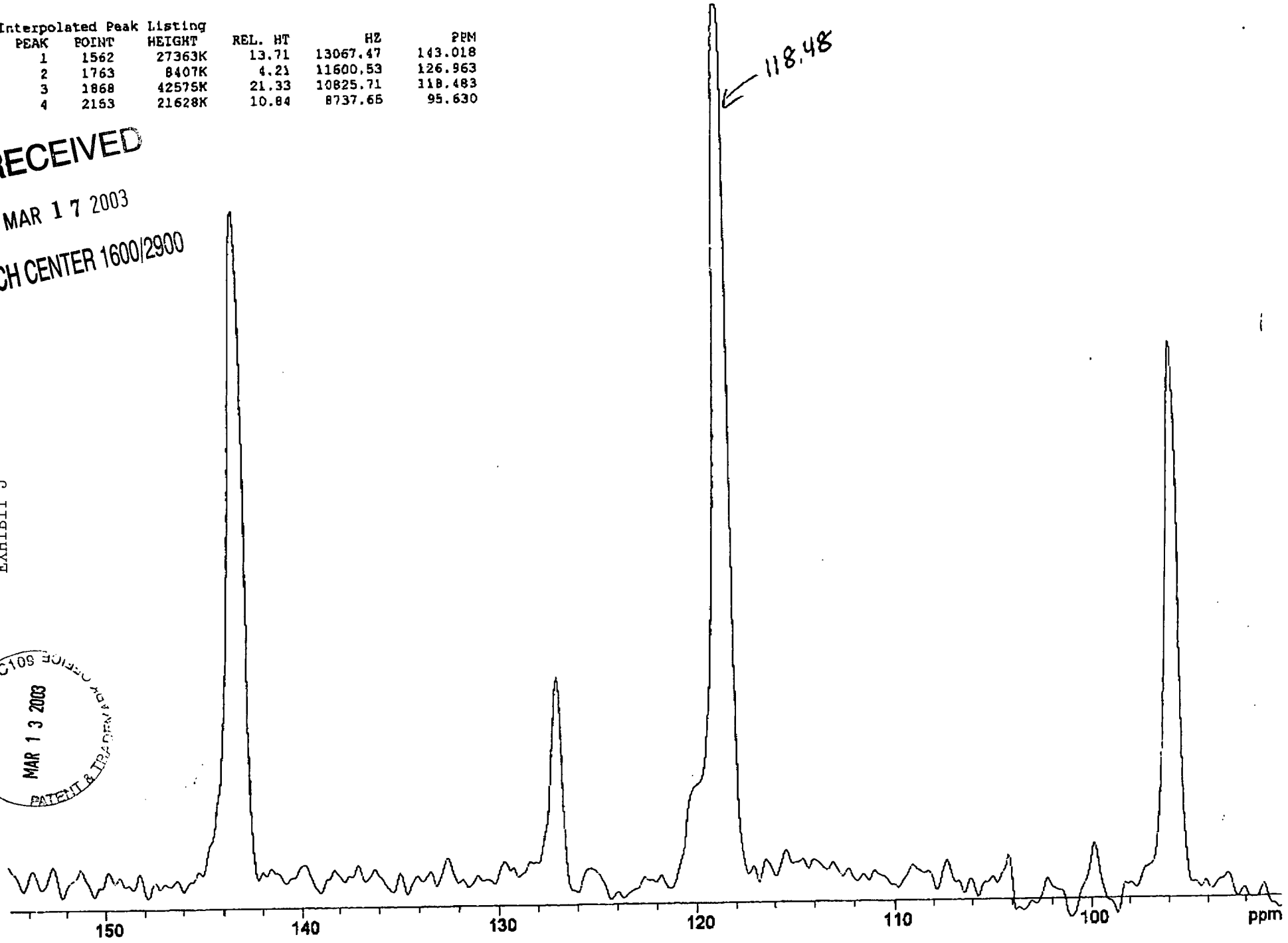
EXHIBIT I



Interpolated Peak Listing

PEAK	POINT	HEIGHT	REL. HT	HZ	PPM
1	1562	27363K	13.71	13067.47	143.018
2	1763	8407K	4.21	11600.53	126.963
3	1868	42575K	21.33	10825.71	118.483
4	2163	21628K	10.84	8737.65	95.630

EXHIBIT J



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SUMMARY

Senior industrial scientist with record of expertise and creative problem solving in the specialty chemical and pharmaceutical industries. Proven laboratory, organizational, communication, supervisory, and innovation skills. Experienced in chemical synthesis, solid-state chemistry, pharmaceutical preformulation, FDA regulatory requirements, engineering principles, manufacturing demands, economics, and patent law. Demonstrated proficiency from idea conception through commercialization.

POSITIONS HELD

SSCI, Inc., West Lafayette, IN

Chief Operating Officer	1997 – present
Vice President for Research and Development	1995 – present

Albemarle (previously Ethyl) Corporation, Baton Rouge, LA

Senior R&D Advisor	1992 – 1995
R&D Advisor	1991 – 1992
Associate-New Product Development and Manager-R&D	1988 – 1991
Research Chemist, Senior Research Chemist, and Senior Research Specialist	1980 – 1988

EDUCATION

Ph.D., Organic Chemistry, University of Maryland, College Park, MD	1979
B.S., Chemistry, University of Maryland, College Park, MD	1974

PUBLICATIONS

Inventor of 40 U. S. patents
Author of 27 technical publications

AFFILIATIONS

American Chemical Society	1975 – present
American Association of Pharmaceutical Scientists	1996 – present
Purdue University, Adjunct Professor in the Department of Industrial and Physical Pharmacy	1995 – present
Topic Editor for the ACS journal *Crystal Growth & Design*	2000 – present

SELECTED ACCOMPISHMENTS

SSCI, Inc., West Lafayette, IN

- In six years expanded SSCI from 1 full-time employee to 60 full-time employees, increasing annual revenue by 2500% from 1996 to 2001. Revenue in 2001 was about $9 M.
- Company leader responsible for all aspects of growth, including staffing, systems design and implementation (project tracking, GMP, LAN, etc), client identification and development, technical output, and R&D program development.
- Initiated and implemented an R&D program which has generated patent-pending technologies.

Albemarle (previously Ethyl) Corporation, Baton Rouge, LA

- Technical group leader responsible for technical leadership, staffing, goal setting, performance evaluation, and safety performance.
- Led a Manufacturing Technology Team that achieved cost reductions and quality improvements for several commercial products.
- Invented an optical purification method that reduced by $10 million the capital cost of manufacturing a commercial chiral product.
- Created a novel, single-crystal x-ray method to design high-efficiency resolving agents. Obtained funding by winning an internal grant, and successfully invented new agents.
- Instituted and supervised basic research programs in core technology areas of organometallic catalysis and flame retardance.
- Established, coordinated, and administered financing of joint research programs with six academic institutions.
- Evaluated market and technical feasibility of the corporation's proposed research projects. Completed market research studies on top candidates.
- Originated and carried out exploratory research leading to new, patented methods for:
  - Synthesis of several bulk pharmaceuticals.
  - Alkylation of nitroaromatics (used at pilot plant scale).
  - Reduced-waste synthesis of unsymmetrical biphenyls.
  - Syntheses of monomers for specialty polymers.
  - Difluoromethylation of carbonyl compounds.
  - Trifluoromethylation of aromatics.
- Invented a series of perfluoroalkylated profen drugs designed to have enhanced lipid solubility.

G. PATRICK STAHLY, Ph.D.

PUBLICATIONS

1. Jarvis, B.B.; Stahly, G.P.; Curtis, C.R. *Cancer Treat. Rep.* **1978**, *62*, 1585. Antitumor Activity of Fungal Metabolites: Verrucarin Beta-9,10-epoxides.
2. Jarvis, B.B.; Stahly, G.P.; Ammon, H.L. *Tetrahedron Lett.* **1978**, 3781. A Novel New Heterocycle from the Reaction of Azide Ion with 2,3-Diphenylthiirene 1,1-Dioxide.
3. Jarvis, B.B.; Stahly, G.P.; Pavanasasivam, G.; Mazzola, E.P. *J. Antibiotics* **1980**, *33*, 256. Structure of Roridin J, A New Macrocyclic Trichothecene from *Myrothecium Verrucaria.*
4. Jarvis, B.B.; Midiwo, J.O.; Stahly, G.P.; Pavanasasivam, G.; Mazzola, E.P. *Tetrahedron Lett.* **1980**, 787. Trichodermadiene: A New Novel Trichothecene.
5. Stahly, G.P.; Ammon, H.L.; Jarvis, B.B. *Acta Cryst.* **1980**, *B36*, 2159. The Structure of 4-[(E)-1,2-Diphenylvinyl]-2,6-diphenyl-1,3,4,5-thiatriazine 1,1-Dioxide.
6. Jarvis, B.B.; Stahly, G.P.; Pavanasasivam, G.; Mazzola, E.P. *J. Med. Chem.* **1980**, *23*, 1054. Antileukemic Compounds Derived from the Chemical Modification of Macrocyclic Trichothecenes. 1. Derivatives of Verrucarin A.
7. Jarvis B.B.; Stahly, G.P. *J. Org. Chem.* **1980**, *45*, 2604. Reactions of 2,3-Diphenylthiirene 1,1-Dioxide with Nucleophiles.
8. Jarvis, B.B.; Pavanasasivam, G.; Holmlund, C.E.; DeSilva, T.; Stahly, G.P.; Mazzola, E.P. *J. Am. Chem. Soc.* **1981**, *103*, 472. Biosynthetic Intermediates to the Macrocyclic Trichothecenes.
9. Jarvis, B.B.; Stahly, G.P.; Pavanasasivam, G.; Midiwo, J.O.; DeSilva, T.; Holmlund, C.E.; Mazzola, E.P.; Geoghegan, R.F. *J. Org. Chem.* **1982**, *47*, 1117. Isolation and Characterization of the Trichoverroids and New Roridins and Verrucarins.
10. Stahly, G.P.; Marlett, E.M.; Nelson, G.E. *J. Org. Chem.* **1983**, *48*, 4423. Selective Hydrolysis-Decarboxylation of Ethyl 1,4-Dimethyl-3-(ethoxycarbonyl)-1H-pyrrole-2-acetate.
11. Stahly, G.P.; Stahly, B.C.; Lilje, K.C. *J. Org. Chem.* **1984**, *49*, 578. Synthesis of 2-(4-Nitroaryl)propionate Esters.
12. Stahly, G.P. *J. Org. Chem.* **1985**, *50*, 3091. Synthesis of Unsymmetrical Biphenyls by Reaction of Nitroarenes with Phenols.
13. Stahly, G.P. *Synth. Commun.* **1987**, *17*, 1053. A Diels-Alder Approach to 4,4'-Thiobis(phthalic acid) Derivatives.
14. Stahly, G.P.; Stahly, B.C.; Maloney, J.R. *J. Org. Chem.* **1988**, *53*, 690. Base-Induced Reactions of Polynitroarenes with Methyl 2-Chloropropionate.
15. Stahly, G.P. *J. Fluorine Chem.* **1989**, *43*, 53. Nucleophilic Addition of Difluoromethyl Phenyl Sulfone to Aldehydes and Various Transformations of the Resulting Alcohols.
16. Stahly, G.P.; Bell, D.R. *J. Org. Chem.* **1989**, *54*, 2873. A New Method for Synthesis of Trifluoromethyl-Substituted Phenols and Anilines.
17. Stahly, G.P. *J. Fluorine Chem.* **1989**, *45*, 431. Trifluoromethylation of 1,3,5-Trinitrobenzene.
18. Stahly, G.P.; Jackson, A. *J. Org. Chem.* **1991**, *56*, 5472. Synthesis of 2-(Perfluoroalkylphenyl)propionic Acids.
19. Stahly, G.P. *Today's Chemist at Work* **1993**, *2*, 28. TLC: An Often Overlooked Tool Giving Speed and Convenience at Low Cost.

G. PATRICK STAHLY, Ph.D.

PUBLICATIONS

20. Manimaran, T.; Wu, T-C.; Klobucar, W.D.; Kolich, C.H.; Stahly, G.P.; Fronczek, F.R.; Watkins, S.E. *Organometallics* **1993**, *12*, 1467. In-situ Generation of Ruthenium-Chiral Phosphine Complexes and Their Use in Asymmetric Hydrogenation.
21. Manimaran, T.; Stahly, G.P. *Tetrahedron: Asymmetry* **1993**, *4*, 1949. Optical Purification of Profen Drugs.
22. Wu, F. J.; Stahly, G. P.; Fronczek, F. R.; Watkins, S. F. *Acta Crystallogr., Sect. C*, **1995**, 18. The Structure of 1,4,7-Tri-*n*-butyl-1,4,7-triazacyclononanechromium Trichloride.
23. Stahly, G.P.; Starrett, R.M. in *Chirality in Industry II*; Collins, A. N.; Sheldrake, G. N.; Crosby, J., Eds.; Wiley & Sons: New York, 1997, Chapter 3. Production Methods for Chiral Non-steroidal Anti-inflammatory Profen Drugs.
24. Stahly, G.P.; McKenzie, A.T.; Andres, M.C.; Russell, C.A.; Byrn, S.R.; Johnson, P. *J. Pharm. Sci.* **1997**, *86*, 970. Determination of the Optical Purity of Ibuprofen Using X-ray Powder Diffraction.
25. Stahly, G.P.; Byrn, S.R. in *Molecular Modeling Applications in Crystallization*; Myerson, A.S., Ed.; Cambridge University Press: New York, 1999, Chapter 6. The Solid-State Structure of Chiral Organic Pharmaceuticals.
26. He, X.; Stowell, J.G.; Morris, K.R.; Pfeiffer, R.R.; Li, H.; Stahly, G.P.; Byrn, S.R. *Crystal Growth & Design* **2001**, *1*, 305. Stabilization of a Metastable Polymorph of 4-Methyl-1,2-nitroacetanilide by Isomorphic Additives.
27. Newman, A.W.; Stahly, G.P. in *Handbook of Pharmaceutical Analysis*; Ohannesian, L.; Streeter, A.J., Eds.; Drugs and the Pharmaceutical Sciences Series 117; Marcel Dekker: New York, 2001, Chapter 1. Form Selection of Pharmaceutical Compounds.